

## Synthesis and Evaluation of Quinoline Carboxyguanidines as Antidiabetic Agents

Dolorès Edmont, Richard Rocher, Christophe Plisson and Jacques Chenault\*

*Institut de Chimie Organique et Analytique, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France*

Received 29 March 2000; revised 19 June 2000; accepted 20 June 2000

**Abstract**—The synthesis and in vivo activities of a series of substituted quinoline carboxyguanidines as a possible novel class of antidiabetic agents is described. © 2000 Elsevier Science Ltd. All rights reserved.

### Introduction

The number of people suffering from diabetes around the world increases day by day. Predictions estimate from 110 million in 1994, numbers will reach 300 million in 2025.<sup>1</sup> About 90% of cases are diabetes of type II (NIDDM), and recent therapies to treat this type of diabetes require the use of oral hypoglycaemic drugs. Amongst the different hypoglycaemic drugs in force at present, guanidine derivatives<sup>2</sup> are often prescribed, the most well known being metformin.

Quinolones, more known for their antibacterial activity, sometimes display hypoglycaemic activity. Indeed, according to Baker and Bramhall<sup>3</sup> in 1972, these molecules act on the glucidic metabolism.

Recent work<sup>4</sup> showed clearly the efficacy of some quinolones in inhibiting the activity of the ATP-K<sup>+</sup> channel of the  $\beta$  cell pancreatic membrane, inducing the production of insulin. These quinolones act according to a mechanism similar to sulfonylureas. Moreover, some molecules of this family, the 7-substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acids, inhibit the aldo reductase enzyme<sup>5</sup> in vivo.

We therefore decided to synthesize some quinolinoyl-guanidines in which some structural modifications have been performed. We also report on the in vivo activities of these compounds as hypoglycaemic agents.

### Chemistry

The 10 synthons with a 4-oxo-1,4-dihydroquinolinic structure **3a–d** and **4d–e**, or a quinolinic structure **5a–c** and **6**, suitable for all further syntheses, have been obtained from commercially available substituted arylamines in three steps as shown in Scheme 1.

The first step involves an enamine bond formation, which was achieved in high yield by condensation of dimethyl acetylenedicarboxylate (DMAD) or ethyl ethoxymethylenemalonate (DEEM) with arylamine **1a–e**. The intermediates fumarate **2a–c** or malonate **2d–e** were then cyclized using diphenylether at reflux.<sup>6</sup>

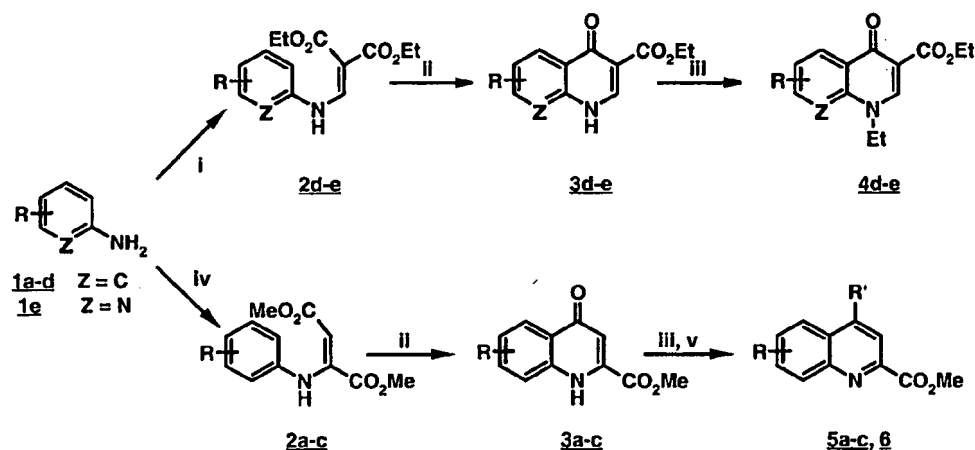
Finally, compounds **4d–e** or **5a–c** were obtained by alkylation with potassium carbonate and ethyl bromide, and compound **6** by chlorination with phosphorus oxychloride.

The carbonylguanidine moiety was introduced by an addition–elimination reaction between guanidine and the ester function<sup>7</sup> of synthons **3a**, **4d–e**, **5a–c** and **6** (Scheme 2). All *N*-[(4-oxo-1,4-dihydroquinolin)carbonyl]guanidine compounds **7**, **8d–e** and **9a**, or *N*-[(quinolin)carbonyl]guanidine compounds **10a–c** and **11a** were isolated as the hydrochloride salt.

In order to assess the importance of each atom in the carbonylguanidine moiety, analogues were also synthesized, including carbonylaminoguanidine, carbonylaminobiguanidine, carbonylaminourea and carbonylaminotetrazole.

We envisaged the formation of both the carbonylaminoguanidine and carbonylaminobiguanidine moiety via a nucleophilic substitution reaction between the amino

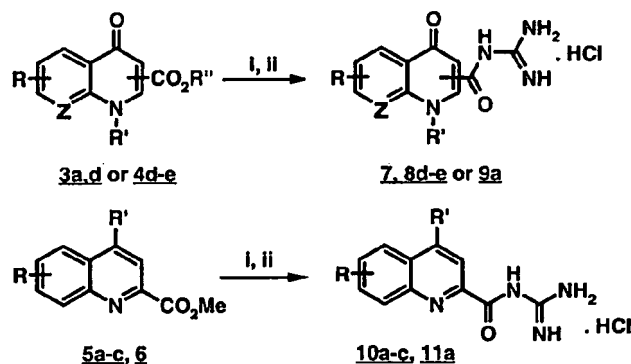
\*Corresponding author. Tel.: +33-2-3849-4588; fax: +2-3841-7281; e-mail: j.chenault@univ-orleans.fr



Scheme 1. (i) DEEM, toluene, reflux; (ii) diphenylether, reflux; (iii) K<sub>2</sub>CO<sub>3</sub>, BrEt, DMF, 50 °C; (iv) DMAD, MeOH, 55 °C; (v) POCl<sub>3</sub>, reflux, 4 h.

## Chemical yields

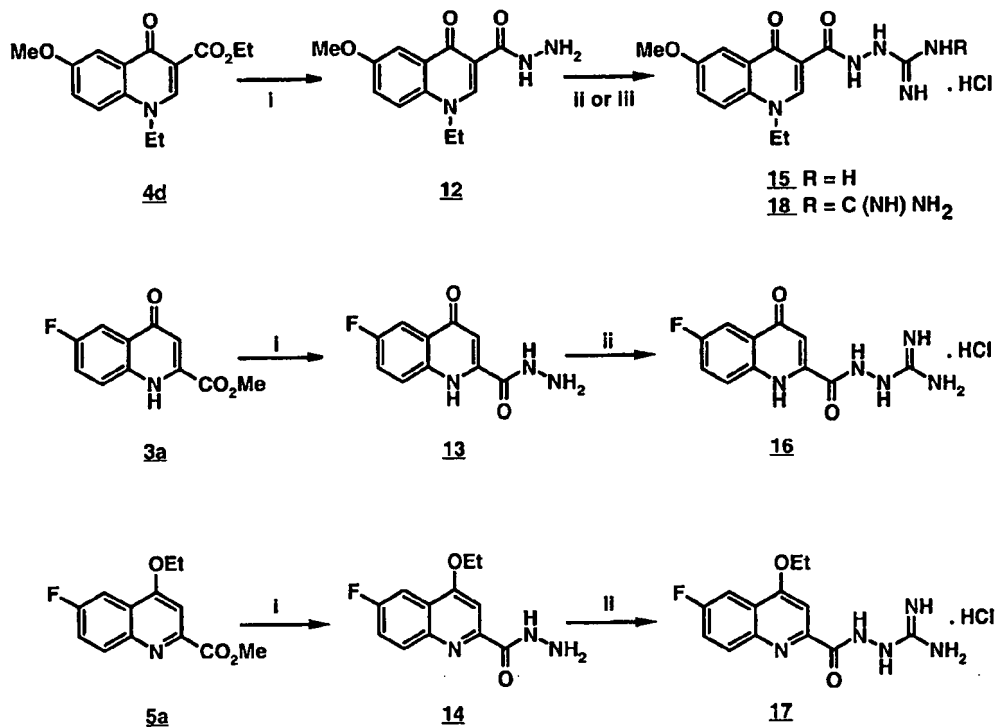
Compound	R	Step 1: condensation (%)	Compound	Step 2: cyclization (%)	Compound	Step 3 (%)	Compound	R'
1a	4-F	86	2a	97	3a	95	5a	OEt
1b	3-OMe	69	2b	64	3b	82	6	Cl
1c	3,4-OCH <sub>2</sub> O	88	2c	76	3c	63	5b	OEt
1d	4-OMe	96	2d	76	3d	98	5c	OEt
1e	6-Me	98	2e	75	3e	90	4d	—
				76	3e	96	4e	—



Scheme 2. (i) Guanidine, DMF, rt, overnight, 2 h for 9a; (ii) EtOH/HCl or HCl aq 10%.

## Chemical yields

Compound	Yield (%)	R/R'/R''/Z/carbonylguanidine position	Compound
3d	92	R=6-OMe, R'=H, R''=Et, Z=C, C3	7
4d	97	R=6-OMe, R'=Et, R''=Et, Z=C, C3	8d
4e	80	R=7-Me, R'=Et, R''=Et, Z=N, C3	8e
3a	87	R=6-F, R'=H, R''=Me, Z=C, C2	9a
5a	86	R=6-F, R'=OEt	10a
5b	89	R=7-OMe, R'=OEt	10b
5c	90	R=6,7-OCH <sub>2</sub> O, R'=OEt	10c
6	79	R=6-F, R'=Cl	11a



Scheme 3. (i)  $\text{NH}_2\text{NH}_2$ , 1.5  $\text{H}_2\text{O}$ , reflux, 2 h; (ii) 1*H*-pyrazole-1-carboxamide hydrochloride, DMF, 100 °C, 3 h; (iii) *N*-amidinopyrazole-1-carboxamide hydrochloride, DMF, 100 °C, 15 min.

## Chemical yields

Compound	Step 1 (%)	Compound	Step 2 (%)	Compound
4d	99	12	60	15
			62	18
3a	69	13	57	16
5a	76	14	76	17

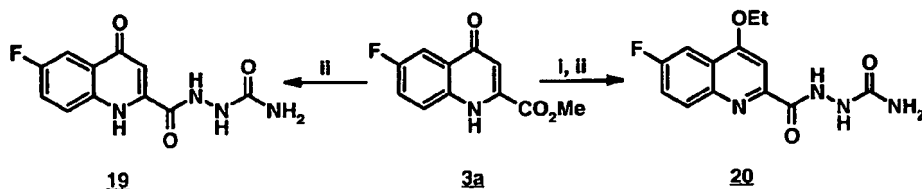
group and 1*H*-pyrazole-1-carboxamide or *N*-amidinopyrazole-1-carboxamide, respectively.<sup>8</sup>

The amidification of compounds 4d, 3a and 5a with hydrazine gives carbohydrazides 12, 13 and 14 (Scheme 3), which are guanylated to give the desired products 15, 16, 17 and 18 in good yields.

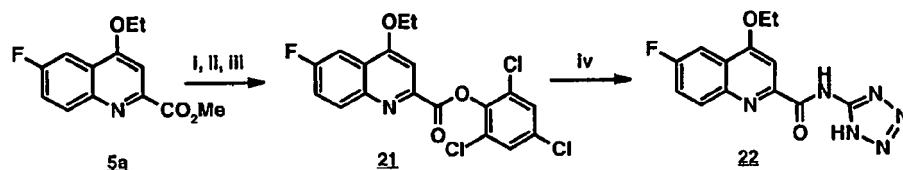
As semicarbazide is commercially available, we expected that the carbonylaminourea moiety would be accessible by condensation from synthons 3a or 5a. Thus, reaction of these compounds with semicarbazide in a mixture of

DMF and dioxane afforded 19 and 20, respectively, in moderate yields (Scheme 4).

Finally, in order to obtain the carbonylaminotetrazole moiety, we initially tried to form the amide bond via condensation of the commercially available 5-amino-tetrazole with the ester function of synthon 5a. The use of an activated 2,4,6-trichlorophenyl ester,<sup>9</sup> in the presence of triethylamine, gave the desired product 22. To this end saponification of 5a, and condensation with 2,4,6-trichlorophenol gave the intermediate ester 21 (Scheme 5).



Scheme 4. (i)  $\text{K}_2\text{CO}_3$ , BrEt, DMF, 50 °C, 4 h, 95%; (ii) semicarbazide, DMF/dioxane, 100 °C, overnight, 58% for 19, 57% for 20.



Scheme 5. (i) NaOH / MeOH, reflux, 2 h, 73%; (ii) SOCl<sub>2</sub>, rt, overnight; (iii) toluene, 2,4,6-trichlorophenol, pyridine, 3 h, 81%; (iv) 5-aminotetrazole monohydrate, acetone, triethylamine, reflux, 2 h, 68%.

Table 1.

Compound	% Glycaemia evolution <sup>a</sup>			
	J1		J4	
	20 mg/kg	200 mg/kg	20 mg/kg	200 mg/kg
15	-10	6	-12	-6
18	-3	2	-2	-5
7	5	-8	3	3
8d	0	0	0	-9
8e	+1	-4	-11	-21
10a	-8	-5	-10	-30
10b	+2	+6	-2	+2
10c	+1	-4	-6	-7
9a	-5	-7	-15	-14
11a	+19	+58	1 death/5	4 deaths/5
16	+8	+8	+4	-2
17	+6	-4	-3	-14
19	-6	-7	-16	-14
20	+3	+8	-8	-3
22	+8	+9	+4	-6

<sup>a</sup>Significant figure.

### Evaluation of the Biological Activity

The antidiabetic activity of compounds 7–9a, 10a–c, 11a, 15–20 and 22 has been determined from a pharmacological test based on the blood glycaemia measure. The results obtained are summarized in Table 1.

Tests were realized from Wistar rats suffering from diabetes type II, which had been brought about by the administration of streptozocin in moderate dose. The glycaemia had been determined on plasma before treatment (J0), then 2 h after a sharp administration (J1) and 2 h after the last administration for 4 days chronic treatment (J4). At the test time, the glucose contribution from the intestine was negligible, as the rats had eaten nothing for 4 h. As the blood samples were taken at the extremity of the tail, the tests were realized on 10 rats at the same time, for each compound at each concentration.

Results from Table 1 show that compound 10a emerges as the most hypoglycaemic agent in the series and has a hypoglycaemic activity superior to metformin (–24% for 200 mg at J4). Changing the different groups on the aromatic ring (10b–c) or at the 4 position (9a and 11a) did not lead to an increase in the hypoglycaemic activity, however the presence of the chloro atom in position 4 resulted in hyperglycaemic activity of the compound 11a. The carbonylguanidine group in position 2 (10a and 9a) confirms that this substituent increases the hypoglycaemic activity comparatively to the 3 position (7 and 8d) as in PZG or AML.<sup>2</sup>

### Acknowledgements

We thank G. Moinet and the Society Lipha-Merck at Chilly-Mazarin for their financial support and in vivo evaluation.

### References and Notes

- Figures from the International Institute of Diabetes (IID), colleague centre of the World Health Organization (WHO).
- A-Rahim, Y.; Beyer, K. H.; Vescell, K. H. E. S. *Pharmacology* 1996, 52, 135.
- Baker, B. R.; Bramhall, R. J. *Med. Chem.* 1972, 15, 233.
- Maeda, N.; Tamagawa, T.; Niki, I.; Miura, H.; Ozawa, K.; Watanabe, G.; Nonogaki, G.; Uemura, K.; Iguchi, A. *Br. J. Pharmacol.* 1996, 117, 372.
- Büyükbıngöl, E.; Das, N.; Klopman, G. *Arch. Pharm.* 1994, 327, 129.
- All new compounds have been fully characterized by mp, IR, MS or <sup>1</sup>H and <sup>13</sup>C NMR spectra. The purities were found to be satisfactory for the pharmacological tests.
- Yamamoto, T.; Hori, M.; Watanabe, I.; Tsutsui, H.; Harada, K.; Ikeda, S.; Ontaka, H. *Chem. Pharm. Bull.* 1997, 45, 1282.
- Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* 1992, 57, 2497.
- Kappe, Th.; Roschger, T.; Färber, G. *J. Heterocycl. Chem.* 1993, 30, 1267.